



## PATENT ABSTRACTS OF JAPAN

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**(54) COMPOSITION FOR PHARMACEUTICAL  
PREPARATION, ITS PREPARATION AND ITS  
PRODUCTION****(57) Abstract:**

**PURPOSE:** To readily obtain the subject preparation having a simple composition and capable of controlling elution of a medicine.

**CONSTITUTION:** In a preparation composed of a medicine exhibiting a pH- dependent solubility and a porous. cellulose, elusion of the medicine is controlled

by supporting an acid or a base on the porous cellulose. The preparation may be carried out by supporting the medicine and an acid or a base on the porous cellulose or by using a coating film containing the medicine and an acid or a base. The composition for pharmaceutical preparation obtained by supporting an acid or a base on the porous cellulose is useful for controlling elusion of the medicine. The preparation may contain an additive such as a binder. A solid preparation such as powder, granule, tablet or capsule can be used as the dosage form.

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**(54) (Title of Invention)**

A composition for pharmaceutical preparation, a pharmaceutical preparation and processes for the production of these.

**(57) (Abstract)**

**Object**

To easily obtain a pharmaceutical preparation which can adjust elution properties of drug by simple composition.

**Construction**

In a pharmaceutical preparation formulated with a drug having different solubility by pH and a porous cellulose species, the solubility of drug is controlled by supporting an acid or base on said porous cellulose species. In pharmaceutical preparation, the drug and an acid or base may be supported on porous cellulose species, or coating layer containing the drug and an acid or base may be formed. A composition for pharmaceutical preparation in which an acid or base is supported on porous cellulose species is useful for controlling the elution properties of drug. Pharmaceutical preparation may contain additives such as binding agent or the like. Pharmaceutical preparation can be used as solid pharmaceutical preparation such as powder, granules, tablet, encapsulated formulation or the like.

**Patent Claims**

**Claim 1**

A pharmaceutical preparation of the kind wherein a drug which has different solubility by pH and a porous cellulose species are formulated, characterised in that the solubility of drug is controlled by supporting an acid or base to said porous cellulose species.

**Claim 2**

A process for the production of pharmaceutical preparation by coating a porous cellulose species with coating layer containing drug and acid or base.

**Claim 3**

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A process for the production of pharmaceutical preparation by supporting drug and an acid or base to porous cellulose species.

**Claim 4**

A composition for pharmaceutical preparation wherein an acid or base is supported on a porous cellulose species.

**Claim 5**

A process for the production of a composition for pharmaceutical preparation wherein an acid or base is supported on porous cellulose species.

**Claim 6**

A solid pharmaceutical preparation containing pharmaceutical preparation in accordance with Claim 1.

**Detailed Description of the Invention**

(0001)

Sphere of Application in Industry

This invention relates to the following, namely, a composition for the pharmaceutical preparation which can adjust solubility and elution properties of physiologically active substance in a sphere of food • pharmaceutical • agrochemical or the like, pharmaceutical preparation using this and a process for production thereof.

(0002)

Technology of the Prior Art

In general, a number of investigations have been carried out on drug release regulation system (drug delivery system) in drugs of food • pharmaceutical • agrochemical or the like. For example, it is proposed in Kokai 56-110612 that a compression moulded substance, wherein specific binding agent and surface active agent or the like are formulated to insoluble drug, thereby the solubility and elution properties of drug are raised. However, because this compression moulded substance needs to be produced by combining many constituents,

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besides fluidised bed granulation method is used, therefore there are many limitations, and at the same time, production operation is complicated.

**(0003)**

In Kokai 56-49314, a pharmaceutical preparation wherein polyethylene oxide is added to formulation compound of drug and specific base agent component, thereby absorbency and durability are improved, is proposed. However, because this pharmaceutical preparation needs to combine many constituents and in addition, the organic solvent needs to be removed, therefore, there are many limitations, and production operation is complicated.

**(0004)**

In Kokai 61-207343, an excipient for pharmaceutical preparation in which fine particulate crystalline cellulose and calcium carbonate are mixed in specific proportion, is proposed. However, during production of this excipient, slurry of each component needs to be spray-dried and it is complicated.

**(0005)**

In Kokoku 5-1796, controlled-release granules wherein plain granules formed by adhesion and binding of a drug, excipient and in accordance with requirements osmotic pressure modifier to a spherical core mainly comprising osmotic pressure modifier made of water soluble organic acid, is coated with gastric fluid insoluble coating layer, is proposed. Because spherical granules of organic acid need to be prepared beforehand in this granule, the production efficiency of granules is easily decreased. Besides, in order to obtained spherical granules with high yield, the production conditions need to be controlled with high precision.

**(0006)**

Moreover, in Kokai 62-30709, in a coating agent in which the drug and swelling agent are coated with a water-insoluble substance, a sustained release pharmaceutical preparation wherein the coating layer is broken-down after a prescribed time by swelling of swelling agent accompanying water absorption, is proposed. However, the swelling agent used in this pharmaceutical preparation is disintegrating agent, and in order to break down coating layer, a

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large quantity of disintegrating agent is required. And, when the quantity added of disintegrating agent increases, the degree of hardness of tablet obtained by compression falls.

(0007)

Moreover, in Kokai 2-105, a tablet formed from a drug and fine powder-form water-insoluble cellulosic polymer is proposed. However, cellulosic polymer must be pulverised to abnormally small fine powder of 5  $\mu$ m or less in order to obtain this tablet, and there is a difficulty in terms of workability.

(0008)

On the other hand, it has been reported by Nakai et al. that when porous cellulose and ethenzamide are mixed and ethenzamide is made non-crystalline by heat-treatment, the elution properties is improved compared to the case using crystalline cellulose (the sixth annual conference of Japan pharmaceutical society, September 26, 1990, Chiba Municipal Hall). However, in order to raise elution properties of ethenzamide in this method, a heat treatment of high temperature of around 100 degrees for about 2 hours is needed, and the productivity of pharmaceutical preparation falls. Moreover, it has been reported that when a mixture of porous cellulose and aspirin was heated under reduced pressure at 50 degrees for three hours, decomposition of the drug occurred [Yonemochi et al. First annual conference of Japan Hospital Pharmaceutical Society, July 20, 1991, Kudan Conference Centre]. As may be clear from this, the drug that can be used is limited in aforesaid process.

(0009)

Moreover, it is disclosed in Kokai 2-84401 that when porous cellulose particle and sublimation drug are mixed and aforesaid drug is absorbed, the elution properties of drug is improved. However, in some cases, aforesaid heat treatment is necessary in order to raise elution properties of drug, besides the rate and duration of dissolution of the drug cannot be controlled. Moreover, it is not possible to cause elution of the drug after a prescribed time.

(0010)

In this way, the elution properties of drug cannot be simply adjusted by any of the prior art

pharmaceutical preparation.

**(0011)**

On the other hand, in Kokoku 56-44777, a production method of a foaming tablet that rapidly breaks down and has excellent moldability with addition of magnesium metasilicate aluminate and crystalline cellulose, is disclosed. As foaming component in this preceding technical literature, a combination of carbonate or bicarbonate with an organic acid such as citric acid, tartaric acid or the like is described. However, the foaming component readily causes sticking during compression moulding as also described in aforesaid preceding technical literature. Therefore a large quantity of lubricant is required.

**(0012)**

Moreover, in order to raise enteric-coated and stomach-solubility of drug, the addition of an acid or base to pharmaceutical preparation containing drug is preferable. However, when an acid and/or base is added, the tableting properties is remarkably lost by the acid and/or base. In particular, squeaking which is the most problematic tableting disorder, is caused, in other words, because the powder has no lubrication properties, the frictional force between compression powder, mortar and pestle becomes strong, and the phenomenon in which pestle and mortar becomes difficult to separate is generated during the tableting, and the productivity greatly falls. In order to improve aforesaid squeaking, a large quantity of lubricant is required in the same way as above, therefore, a large limitation is accompanied in the design of pharmaceutical preparation.

**(0013)**

Problems to be Overcome by this Invention

Accordingly, the object of this invention is to put forward a pharmaceutical preparation which can easily adjust elution properties of drug.

**(0014)**

Another object of this invention is to put forward a pharmaceutical preparation in which the dissolution rate and duration of drug are controlled.

**(0015)**

Yet another object of this invention is to put forward a process for the production that can easily produce a pharmaceutical preparation composition and pharmaceutical preparation having aforesaid excellent characteristics by simple composition.

**(0016)**

Another object of this invention is to put forward a process for the production that can obtain pharmaceutical preparation with good efficiency in spite of containing an acid or base.

**(0017)****Construction of the Invention**

These inventors carried out assiduous investigations, as a result, discovered that when a composition containing porous cellulose species and an acid or base was pharmaceutically formulated together with drug, the solubility and elution properties of drug were simply controlled by the action of porous cellulose species and the acid or base. This invention was completed as a result of this.

**(0018)**

In other words, this invention puts forward a pharmaceutical preparation of the kind wherein a drug which has different solubility by pH and a porous cellulose species are formulated, characterised in that the solubility of drug is controlled by supporting an acid or base to said porous cellulose species.

**(0019)**

This invention also puts forward a process for the production of a pharmaceutical preparation by coating a porous cellulose species with coating layer containing drug and acid or base, or by supporting drug and an acid or base to porous cellulose species.

**(0020)**

This invention also puts forward a composition for pharmaceutical preparation wherein an acid

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or base is supported on a porous cellulose species, and a process for the production of a composition for pharmaceutical preparation wherein an acid or base is supported on porous cellulose species.

**(0021)**

This invention puts forward a solid pharmaceutical preparation containing aforesaid pharmaceutical preparation.

**(0022)**

Moreover, the "support" and "support layer" in this invention means the case wherein it is partially supported not only the whole surface of the porous cellulose species and also includes the case wherein it is adsorbed, absorbed or coated. The "coating layer" may not be a continuous layer that cover the whole surface of the porous cellulose species but is used including the case wherein it is partially coated.

**(0023)**

As aforesaid porous cellulose species, for example, a porous cellulose species obtained by addition of a liquid mixture of viscose and foaming agent such as calcium carbonate or the like to solidification liquid, thereby simultaneously carrying out condensation • regeneration of cellulose species and decomposition of foaming agent [Fujita et al. Chemical Engineering Society the 23rd Autumn Conference Text (October 21, 2000), Kanazawa University], porous cellulose species disclosed in Kokai 64-43530, Kokai 1-167345, Kokai 1-188539, Kokai 1-272643, Kokai 2-84401, Kokai 2-208330 and Kokai 2-2081331, furthermore, porous cellulose species wherein hemp cellulose is enzyme-treated, mineral acid treated, and the like are nominated. These porous cellulose species may be crystalline or non-crystalline.

**(0024)**

The hole structure of these porous cellulose species is not limited in particular, and for example, a structure wherein many radiating small holes are formed in cross section (hereinafter may be called A type), a structure wherein large holes are formed (hereinafter may be called B type), or a mixture of small holes and large holes may be adopted. The holes may



be continuously connected, or may be independent.

**(0025)**

The shape of porous cellulose species can be selected corresponding to applications of pharmaceutical preparation. When pharmaceutical preparation is solid oral administration agent, it may be any shape of granular, quadrate, spherical, elliptical, a flattened form, cylindrical, hollow cylindrical or the like. Usually granular porous cellulose species is frequently-used.

**(0026)**

The size, pore size and distribution of granular porous cellulose species can be selected corresponding to desired floating property, controlled-release or the like of the drug. Average particle diameter of preferred granular porous cellulose species is for example around 0.001-10 mm, and average pore size distribution is 0.0001-150  $\mu\text{m}$ , preferably 0.001-150  $\mu\text{m}$ . Moreover, bulk specific gravity of preferred porous cellulose species is 0.01-0.8 g/ml approximately. The composition of porous cellulose species is not limited to cellulose simple substance and may be a composite particle with chitin, a cellulose imparted with various functional groups (for example diethylaminoethylation cellulose, carboxymethylation cellulose or the like).

**(0027)**

Among such porous cellulose species, there is a species which shrinks in dried condition and also has small specific gravity and on contact with moisture, it is swollen and volume is increased.

**(0028)**

The composition for pharmaceutical preparation of this invention contains aforesaid porous cellulose species and an acid or base. A composition for pharmaceutical preparation may contain both components of acid and base, and may contain additives described hereinafter of appropriate quantity.

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**(0029)**

As acid and base, various compounds permitted in pharmaceutical preparation can be used.

**(0030)**

As acid, for example, a mineral acid such as hydrochloric acid or the like, an organic acids such as acetic acid, citric acid, tartaric acid, succinic acid, maleic acid, fumaric acid, ascorbic acid or the like, a clay mineral such as acid clay or the like, silica alumina, cation-exchange resin, intestine soluble base and a solid acid such as aluminium oxide and the like, are nominated. As aforesaid intestine soluble base, acidic polymers, for example, hydroxypropyl methyl cellulose phthalate, cellulose acetate phthalate, carboxymethylethyl cellulose (trade name CMEC AQ, made by Kojin), methacrylic acid-methyl methacrylate copolymer [Eudragit L100-55, Eudragit L100, Eudragit S100 made by Rohm Pharma company (Germany)] and the like are exemplified. At least a kind of these acids is used. As preferred acid, an acid of solid form is included.

**(0031)**

The quantity added of acid with respect to porous cellulose species can be selected corresponding to the acidity of acid, dissolution rate or the like of desired drug and usually it is 0.1-95 wt.% in the whole quantity of porous cellulose species and acid, preferably 1-90 wt.% approximately. When the quantity added of acid is less than 0.1 wt.%, the control of solubility and elution properties by acid is not adequate, and when 95 wt.% is exceeded, it becomes an excess quantity.

**(0032)**

As base, solid bases such as oxides, hydroxides, carbonates, hydrogen carbonate, inorganic acid salts, organic salts of Group I, II, III, metal of Periodic Table, and the like are nominated. For example, as embodiment of base, sodium hydroxide, potassium hydroxide, calcium hydroxide, barium hydroxide, magnesium hydroxide, aluminium hydroxide, calcium oxide, barium oxide, magnesium oxide, sodium carbonate, potassium carbonate, calcium carbonate, barium carbonate, magnesium carbonate, sodium bicarbonate, potassium hydrogencarbonate, magnesium silicate, aluminium silicate, silicic acid (Syloid, Aerosil), magnesium metasilicate

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aluminate (Neusilin), magnesium stearate, aluminum stearate, sodium stearate and the like or mixture thereof or the like are nominated. At least one kind of these base can be used. A solid base is included in preferred base.

**(0033)**

The quantity added of base with respect to porous cellulose species can be selected corresponding to basicity of base, desired dissolution rate or the like of the drug and it is usually 0.1-80 wt.% in the whole quantity of porous cellulose species and base, preferably 1-75 wt.% approximately. When the quantity added of base is less than 0.1 wt.%, the control of solubility and elution properties of drug are not adequate, when 80 wt.% is exceeded, it becomes an excess quantity, and also there is a situation that the porous structure of porous cellulose species is destroyed.

**(0034)**

The pharmaceutical preparation that uses such composition for pharmaceutical preparation brings various kinds of merits.

**(0035)**

For example, when a composition for aforesaid pharmaceutical preparation is pharmaceutically formulated with the drug, the solubility of drug can be controlled, and in addition, when a drug soluble in acid is combined and formulated with organic acid, the organic acid is rapidly eluted in stomach. Accordingly, the drug can be absorbed in a person with an acidity who is generally said to have poor absorption, in the same way as in an ordinary person. On the other hand, when a drug which is hard to dissolve in acid is formulated, although the elution properties in stomach falls, the elution properties of drug are improved by aforesaid porous cellulose species, therefore the elution and absorption of drug can be continued. When a drug soluble in base or a drug which is hard to dissolve in base is formulated, the elution properties and absorbable of drug can be controlled in the same way as above.

**(0036)**

When a basic drug is used in combination with acid, or when an acidic drug is used in

combination with base, the elution of drug in the drug can be promoted in both stomach and intestine. Moreover, the combination of acidic drug with acid can inhibit the elution of drug in stomach, and can promote elution of drug in intestine. The combination of base and basic drug promotes elution of drug in stomach, and inhibits the elution of drug in intestine. Moreover, when a neutral drug is used, there is a situation that drug is stabilised by aforesaid acid or base.

**(0037)**

Moreover, among the pharmaceutical preparations including aforesaid porous cellulose species, aforesaid composition for pharmaceutical preparation and drug, there is a species which is contacted in dry state but wherein the volume of porous cellulose species is rapidly increased on contact with water or the like. This characteristic is used, and for example, when aforesaid porous cellulose species, composition for pharmaceutical preparation or pharmaceutical preparation is coated with water-insoluble coating layer, the porous cellulose species is remarkably swollen by the moisture that passed through aforesaid coating layer and penetrated inside, and the coating layer is burst by large swelling force thereof. Moreover, this rupture of coating layer may occur in an explosive manner. Accordingly, in oral administration, a pharmaceutical preparation wherein the drug is eluted after a prescribed time or a targeting pharmaceutical preparation wherein the drug is dissolved and absorbed at a specific site in digestive tract can be formed.

**(0038)**

Moreover, when it is coated with tough coating layer and coating layer of strong resilience, the moisture that passed through coating layer is absorbed by porous cellulose species, a sustained pharmaceutical preparation in which the drug is gradually discharged by high swelling force thereof can be obtained. A pharmaceutical preparation having such characteristic can be used not only as oral agent but also as suppository. In this case, the pharmaceutical preparation swells in rectal part, remains at the same position for a long time and the drug efficacy can be increased.

**(0039)**

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Moreover, for example, when an enteric coating is provided on the porous cellulose species formulated with a base, the base formulated together with porous cellulose species is dissolved by the moisture which penetrated, and the coating layer can be dissolved from the inside of the coated pharmaceutical preparation together with dissolution of drug and high osmotic pressure. Therefore, drug is rapidly discharged in small intestine. Conversely, when a stomach-soluble coating layer and acid are combined and pharmaceutically formulated, the stomach-soluble coating layer coated for the purpose of for example masking is rapidly destroyed, and drug is rapidly eluted.

**(0040)**

Moreover, there is a situation that the drug is stabilised by addition of aforesaid acid and/or base. Moreover, when the formulation characteristics of drug and an acid and/or base is poor, compositions containing each component or stabilised drug are combined, and admixed to porous cellulose species and it can be pharmaceutically formulated.

**(0041)**

The pharmaceutical preparation of this invention contains at least aforesaid porous cellulose species, drug and an acid or base. More particularly drug having different solubility by pH and the porous cellulose species are formulated, and an acid or base is supported on said porous cellulose species. By this, solubility of drug can be controlled.

**(0042)**

Aforesaid drug having different solubility by pH includes various kinds of substances having physiological activity, for example food such as various vitamin species, mineral species, amino acid species or the like or additives for food, cattle feed, agrochemical drug such as pesticide, bactericide or the like and the like. Preferred drug is a medicinal drug.

**(0043)**

As drug, for example as central nervous system drug, diazepam, idebenone, aspirin, ibuprofen, piroxicam, diclofenac, indomethacin, sulindac, lorazepam, nitrazepam, acetaminophen, ketoprofen or the like, as circulatory organ system drug, molsidomine, vinpocetine, methyldopa,

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atenolol, metoprolol, captopril or the like, as respiratory system drug, 3-(imidazo [1,2-b] pyridazin-6-yl) oxy-2,2-dimethylpropane sulphonamide hydrochloride (hereinafter it may be described as compound A), amlexanox, dextromethorphan, theophylline, pseudoephedrine or the like, as alimentary system drug, benzimidazole series drug such as lansoprazole, omeprazole or the like, bisacodyl, 5-aminosalicylic acid or the like, as antibiotic and chemotherapeutic drug, ceftiofur hydrochloride, cephalexin, cefaclor, cefradine, amoxicillin, dicloxacillin or the like, as metabolism system drug, lysozyme chloride, adenosine triphosphate, glibenclamide, potassium chloride or the like, as vitamin series drug, vitamin B1, vitamin B2, vitamin B6, vitamin C, fursultiamine or the like vitamin A, oil state agent such as vitamin E, liquid such as herbal medicine extract or the like and slurry state agent, other metabolic drug, vitamin species, herbal medicine, extract species, the antacid or the like which have different solubility by pH, are nominated. These drugs can be used as one kind of or two kinds or more.

**(0044)**

Aforesaid drug may be co-used with additives. As additives, the conventionally used component which is generally used for producing orally-administered solid pharmaceutical preparation, for example excipient such as lactose, corn starch, sucrose, talc, crystalline cellulose, mannitol, light anhydrous silicic acid, magnesium carbonate, calcium carbonate, L-cysteine or the like, binding agent such as hydroxypropylcellulose (hereinafter, it may be called HPC), hydroxypropyl methyl cellulose, pregelatinised starch, partly pregelatinised starch, methyl cellulose, carboxymethylcellulose, polyvinylpyrrolidone, pullulan, dextrin, gum arabic or the like, disintegrating agent such as carboxymethylcellulose calcium, low degree of substitution hydroxypropylcellulose (hereinafter, it may be called L-HPC), starch species, crosslinked carboxymethylcellulose sodium, crosslinked insoluble polyvinylpyrrolidone or the like, surface active agent such as for example anionic system surface active agent such as alkyl sulphate sodium or the like, non-ionic surface active agent such as polyoxyethylene sorbitan fatty acid ester, polyoxyethylene fatty acid ester and polyoxyethylene castor oil derivative or the like, colorant such as titanium oxide, red iron oxide, tar pigment or the like, corrigents such as l-menthol, peppermint oil or the like, and the like are nominated. Moreover, masking of taste, a barrier controlling transition of moisture and water, separation between drug

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and/or additives, intestine soluble, stomach soluble or insoluble base for coating layer formation to give intestine soluble, stomach-soluble properties and the like are including in additives. Two kinds or more of these additives may be used. Moreover addition of surface active agent has an effect to raise elution properties of the drug.

**(0045)**

Pharmaceutical preparation of this invention contains drug, an acid and/or base in various forms. In other words, porous cellulose species is used as carrier such as adsorbent or the like, and drug and an acid and/or base are supported on porous cellulose species and support layer may be formed.

**(0046)**

Moreover, the porous cellulose species is used as nucleus, and porous cellulose species may be coated with coating layer containing the drug and an acid and/or base.

**(0047)**

Moreover, at least one supported layer and coating layer may be formed on porous cellulose species in any order. In these case, it is preferred that at least one of the aforesaid supported layer and coating layer contains drug and an acid and/or base, but at least one of the aforesaid supported layer and coating layer may contain drug and the other may contain an acid and/or base. Moreover, aforesaid porous cellulose species may be coated with plurality of coating layers. In this case, at least one coating layer may contain drug and an acid and/or base, and drug and the acid and/or base may be contained in the different coating layers to each other.

**(0048)**

Porous cellulose species is used as an additive, and porous cellulose species, drug and an acid and/or base may be mixed.

**(0049)**

In these cases, aforesaid supported layer, coating layer and admixture may contain aforesaid additives and substrate for coating layer formation.

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**(0050)**

Moreover, in such pharmaceutical preparation, stomach-soluble, enteric-soluble or water-insoluble coating layer, coating layer of aforesaid sustained pharmaceutical preparation using swelling properties of porous cellulose species with moisture or coating layer of said targeting pharmaceutical preparation or the like may be applied.

**(0051)**

Support of drug and an acid and/or base can be carried out by adsorption to porous cellulose species and by coating to porous cellulose species or the like. Moreover, mixing can be carried out by mixing or combining of porous cellulose species, drug and an acid and/or base. In such cases, in accordance with requirements aforesaid additives and substrate may be co-used.

**(0052)**

Aforesaid coating layer can be formed using coating agent containing substrate for coating layer formation corresponding to the object. For example, as substrate, hydroxypropyl methyl cellulose, ethyl cellulose, hydroxymethyl cellulose, HPC, L-HPC, polyoxyethylene glycol, Tween 80, Pluronic F68, castor oil, cellulose acetate phthalate, hydroxypropyl methyl cellulose phthalate, hydroxymethyl cellulose acetate succinate, acrylic acid copolymer, carboxymethylethyl cellulose, polyvinylacetal diethylamino acetate, shellac and waxes, and dye such as talc, titanium oxide, red iron oxide or the like are nominated. At least one species of these substrates can be used.

**(0053)**

The content of drug in pharmaceutical preparation can be selected according to the form of pharmaceutical preparation, existence of co-used additive. When a drug is contained in supported layer, the content of drug is for example 0.01-100 wt.%, preferably 0.1-100 wt.% approximately. Moreover, when the drug is contained in coating layer, the content of drug is 0.01-97 wt.%, preferably 0.1-95 wt.% degree.

**(0054)**



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The size of pharmaceutical preparation of this invention can be selected corresponding to applications, and when it is powder, the particle diameter thereof is usually substantially 500  $\mu\text{m}$  or less. Even with a pharmaceutical preparation having small particle diameter, solubility, elution properties or the like of drug can be controlled by combining aforesaid porous cellulose species and an acid and/or base.

(0055)

Below it is described in greater detail about a process for the production of a composition for pharmaceutical preparation and pharmaceutical preparation of this invention. Moreover the process for the production of a composition for pharmaceutical preparation and the process for the production of pharmaceutical preparation are substantially different in terms of the existence of drug. Accordingly, the process for the production of pharmaceutical preparation is described with a composition for pharmaceutical preparation in below.

(0056)

In these processes for the productions, porous cellulose species can be used as carrier as adsorbent, additive or nucleus.

(0057)

When porous cellulose species is used as adsorbent, at least drug and an acid and/or base are supported by adsorption, absorbency, coating. When water soluble drug and an acid and / base are dissolved in water and added to porous cellulose species, this is useful to decrease the fluctuations of the content of the drug and acid and/or base. The drug and an acid and/or base having low solubility with respect to water are dissolved in a solvent formed from organic solvent such as ethanol or the like or a solvent such as pH buffer or the like and this may be used as liquid mixture. In these cases, an acid and/or base, other drug and additive are contained in liquid mixture including drug, it may be supported to porous cellulose species, and a liquid mixture containing drug and a liquid mixture containing acid and/or base or the like may be used separately and supported. Moreover, the supporting of drug or the like to porous cellulose species may be carried out repeatedly using a dilute liquid mixture.

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**(0058)**

For supporting drug or the like on porous cellulose species, aforesaid liquid mixture is added to the porous cellulose species which had been introduced into tumbling granulator, stirring granulator, fluidised bed granulation machine, centrifugation tumbling granulator or the like. When a granulator of tumbling motion and stirring type is used, a fluid volume that does not exceed the adsorption power of porous cellulose species is used. Adsorption power of porous cellulose species differs depending on the kind of liquid mixture, when the solvent is water and organic solvent, for example, it is around 1-13 times of porous cellulose species. On the other hand, a granulator of flow and centrifugation rolling motion flow type is used, liquid mixture is sprayed under condition wherein the porous cellulose species is fluidised under wet state.

**(0059)**

A composition for pharmaceutical preparation and pharmaceutical preparation are obtained by drying porous cellulose species of wet state after supporting treatment with a conventional method such as vacuum, flow, freeze and heat or the like.

**(0060)**

When the solubility of drug and acid and/or base with respect to water is low, using process such as ordered mixture by mechanical impulse, aforesaid component may be supported by adsorption or the like. When the drug or the like is supported by mechanical impulse, ball mill type, hammer mill type, of rolling motion compression type instruments are used and, a suitable solvent is introduced with dry process, and is absorbed, are adsorption powder can be produced.

**(0061)**

When porous cellulose species is used as additive, pharmaceutical preparation is obtained by mixing porous cellulose species with drug and an acid and/or base, and additive in accordance with requirements. This process is useful when the content of drug, an acid and/or base and additive are large or when it is difficult to apply aforesaid process.

**(0062)**

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Mixing of porous cellulose species and drug or the like is preferably carried out by stirring granulation or roller-granulation. The content of porous cellulose species in admixture, is preferably for example, 5 wt.% or more. When it is less than 5 wt.%, swelling power of admixture is small, and the control of solubility and elution properties of drug is difficult.

**(0063)**

When the porous cellulose species is used as nucleus, the coating agent containing substrate, drug and an acid and/or base is used, and coating film including drug and an acid and/or base may be provided on porous cellulose species. Moreover, a coating agent for coating layer formation and a liquid mixture for forming the support layer are sprayed and coated to porous cellulose species in an arbitrary order, and thereby a coating film and a support layer may be formed. In this case, the drug and/or (an acid and/or base) is contained in at least one of the coating agent for aforesaid coating layer formation and liquid mixture for forming support layer. Moreover, the liquid mixture may contain an acid and/or base, binding agent and additive and may be either of solution or liquid dispersion. Moreover, the adsorption of drug or the like is produced, too on spraying and coating process of said coating agent and liquid mixture.

**(0064)**

Moreover, in another method, powdery dusting powder may be sprinkled while spraying a liquid mixture to nucleus. In this case, the binding agent is included in at least either of the liquid mixture and powdery dusting powder, and the drug and an acid and/or base are included in the other. Moreover, the liquid mixture containing drug and powdery dusting powder including an acid and/or base may be used with binding agent, and a liquid mixture including an acid and/or base and powdery dusting powder including drug may be used with binding agent. Furthermore, other additives may be contained in the liquid mixture and powdery dusting powder. With these processes, the coating layer can be formed with a simple procedure by sprinkling over powdery dusting powder. Moreover, when powdery dusting powder including at least one species of drug and an acid and/or base is sprinkled while spraying the liquid which include at least binding agent and does not include drug, the coating layer can be readily formed even if the drug is easily lose its stability with respect to the solvent contained in the liquid mixture. Usually grain size of dusting powder is 100  $\mu\text{m}$  or less, preferably about 50  $\mu\text{m}$

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or less. Moreover, powdery dusting powder in which drug, an acid and/or base, and additive in accordance with requirements are mixed, is added without using liquid mixture, and the porous cellulose species may be coated using dry process.

**(0065)**

On the other hand, when two or more drugs and acid and/or base with poor formulation characteristics are coated, the coating may be carried out using each liquid mixture and powdery dusting powder including additives in accordance with requirements simultaneously or separately, and support layer and/or coating layer interval may be shielded by a coating layer. Moreover, the porous cellulose species in which drug or the like was supported on by using the like of adsorption, it may be coated using a liquid mixture and powder dusting powder including at least a drug having poor formulation characteristics with respect to aforesaid drug. This process is useful for obtaining a pharmaceutical preparation including two kinds or more drugs having differing elution time.

**(0066)**

The quantity of binding agent added with respect to the mixed liquid is different depending on drug or quantity added or the like of additive, usually it is 0.1-70 wt.%, preferably 0.5-30 wt.% approximately. When the quantity of binding agent added is less than 0.1 wt.%, the binding power of drug with respect to nucleus and acid and/or base is small, and when 70 wt.% is exceeded, viscosity of liquid mixture increases, and production workability is easy to fall.

**(0067)**

Moreover, using a liquid mixture and powder dusting powder including coating agent, binding agent including base, the porous cellulose species may be coated in more than one coated layers. In this case, the substrates having different contained proportion and viscosity grade or the like are selected, or a liquid mixture in which the drug, acid and/or base and proportion of other additive are changed are used, and it is coated successively, and the contained proportion of substrate and the like in the support layer of the nucleus and/or coating film, the concentration of drug, acid and/or base are changed successively or stepwise. In this case, for example, as a liquid mixture, a solution or liquid dispersion having the content of binding agent

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in the outside range of 0.1-70 wt.% may be used.

**(0068)**

Moreover, when an acid and/or base, other drug and other additives are dissolved or dispersed in coating agent and liquid mixture, the formulated proportion thereof may be changed.

**(0069)**

In these processes, for example, it can be carried out using conventionally used apparatus such as centrifugation rolling motion type fluidised bed granulation machine, fluidised bed granulation machine, stirring granulator or the like.

**(0070)**

Moreover, aforesaid process is repeated, aforesaid processes are combined suitably, and pharmaceutical preparation composition and pharmaceutical preparation may be produced. For example, aforesaid porous cellulose species is coated with coating agent including base beforehand, thereafter, it may be subjected to absorptive treatment of drug and an acid and/or base or the like, or the granulation powder coated using aforesaid liquid mixture together with adsorption powder after drying or absorptive treatment, an admixture or powdery dusting powder may be coated with a coating agent. Moreover, coating by coating agent may be carried out in the middle of absorptive treatment. Moreover, coating layer may be formed using coating agent including substrate between plurality of coating layer and between coating layer and support layer in order to shield and separate drug and acid and/or base. Moreover the obtained pharmaceutical preparation may be mixed with acid and/or base, other drug and/or additive.

**(0071)**

A coating by coating agent may be carried out using conventional method to the pharmaceutical preparation obtained in this way, in order to mask the taste, to impart intestine soluble stomach-soluble or to control elution properties of drug or the like.

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(0072)

Solid pharmaceutical preparation of this invention can be used as powder without further treatment as aforesaid pharmaceutical preparation. Moreover, according to conventional method, it may be granule and tablet in which the pharmaceutical preparation is added to granule and tablet, and solid pharmaceutical preparation may be the encapsulated formulation which is packed into capsule. Moreover, pharmaceutical preparation is introduced into container beforehand and may be used as solid agent to which water is added in accordance with requirements.

(0073)

Advantages Afforded by this Invention

Because the composition for pharmaceutical preparation of this invention contains porous cellulose species and an acid or base, it is simply possible to control elution properties of drug in the pharmaceutical preparation.

(0074)

Because the pharmaceutical preparation of this invention contains porous cellulose species and drug and acid and/or base, it is possible to control dissolution rate and duration of drug.

(0075)

In the process for the production of this invention, pharmaceutical preparation composition and pharmaceutical preparation having excellent characteristic such as above-mentioned can be produced simply and also with simple composition by a simple procedure such as supporting an acid and/or base and drug to porous cellulose species, applying coating layer or the like.

(0076)

Moreover, with a process for the production of this invention, a pharmaceutical preparation having excellent tableting properties can be obtained efficiently in spite of including an acid and/or base.

(0077)

**Examples**

Hereinafter, this invention is described in greater detail based on Examples, Comparative Examples and Test Examples. However, this invention is not restricted to these.

**(0078)****Example 1**

Spherical porous cellulose (hole of structure A type, bulk specific gravity 0.2 g/ml, a diameter of 0.3 mm diam.) 12.5 g was introduced into a mortar, and a solution in which citric acid 12.25 g and vinpocetine 0.25 g were dissolved in water 20 ml beforehand was added, it was mixed lightly with a spatula, and it was absorption-treated. Thereafter, it was dried at 40 degrees for 16 hours under vacuum, and adsorption powder was obtained.

**(0079)**

The obtained adsorption powder was swollen in three or four times under wet condition, however, it was re-constructed to the original diameter by drying.

**(0080)****Example 2**

Spherical porous cellulose (hole of structure B type, bulk specific gravity 0.2 g/ml, a diameter of 0.3 mm diam.) 25 g were introduced into a mortar, a solution in which citric acid 50 g was dissolved in water 90 ml beforehand was added, it was mixed lightly with a spatula, and it was absorption-treated. Thereafter, it was dried at 40 degrees for 16 hours under vacuum, and adsorption powder was obtained.

**(0081)**

The obtained adsorption powder was swollen in three or four times under wet condition, however, it was re-constructed to the original diameter by drying.

**(0082)****Example 3**

Adsorption powder was obtained in the same way as in Example 2, except that sodium

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carbonate was used instead of citric acid and absorption-treatment was carried out three times by dividing the solution.

(0083)

**Example 4**

Spherical porous cellulose (hole of structure A type, bulk specific gravity 0.1 g/ml, a diameter of 2.0 mm diam.) 380 g were introduced into a flow type coating granulator (FD-3S made by Powrex Co.) and coating was carried out by spraying bulk liquid of following composition prepared beforehand with a bottom spray system while controlling air-blow temperature of 70 degrees and product temperatures of about 40 degrees. Spray was stopped at a point in time that prescribed quantity of bulk liquid was sprayed, and drying was carried out for one minute without any further treatment, and thereafter, it was classified with a circle sieve of 32 mesh, and granule of 480 g was obtained.

(0084)

Bulk liquid

Compound A	5 g
Tartaric acid	5 g
Lactose	20 g
Talc	20 g
L-HPC	20 g
HPC (type M, viscosity 300 cps)	6 g
HPC (type L, viscosity 8 cps)	44 g
Water	1080 g

**Comparative Example 1**

Lactose 100 kg, starch 20 kg and vinpocetine 5 kg were introduced into a fluidised bed granulation dryer (STRE-M5 made by Powrex Co.) and it was granulated by spraying an aqueous solution 60 kg in which hydroxypropylcellulose 5 kg was dissolved beforehand with the top spray system while controlling air-blow temperature 90 degrees and product temperatures of about 40 degrees, and granulation was obtained by drying it.

(0085)



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### Comparative Example 2

Citric acid 100 mg was mixed to granule 52 g obtained in Comparative Example 1, and mixed powder was prepared.

(0086)

### Comparative Example 3

Crystalline cellulose (Abicel made by Asahi Chemical Industry Co, Ltd.) 12.5 g, citric acid 12.25 g and vinpocetine 0.25 g were introduced into a mortar, water 5 ml was added, and it was kneaded with using a pestle. Thereafter, it was dried at 40 degrees for 16 hours under vacuum, and kneaded powder was obtained.

(0087)

### Comparative Example 4

Crystalline cellulose (Abicel made by Asahi Chemical Industry Co, Ltd.) 25 g and citric acid 50 g were introduced into a mortar, water 10 ml was added, and it was kneaded with using a pestle. Thereafter, it was dried at 40 degrees for 16 hours under vacuum, and kneaded powder was obtained.

(0088)

### Test Example 1

The elution properties of adsorption powder 200 mg obtained in Example 1, granules 52 mg obtained in Comparative Example 1 and mixed powder 152 mg obtained in Comparative Example 2 was investigated with the eleventh amendment Pharmacopoeia of Japan • general assay 46 elution test method • the second method (75 rpm). The test liquid used was 500 ml of the second liquid of Pharmacopoeia of Japan • general assay 38 disintegration test method. The test results are shown in Table 1.

(0089)

Table 1

Elution time (mins)	Elution rate (%)				
	1	5	10	30	60
Example 1	83	99	100	100	100

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Comparative Ex 1	11	25	30	40	47
Comparative Ex 2	32	46	49	56	60

As may be seen from Table 1, pharmaceutical preparation obtained in Example 1, in spite of the liquid properties wherein the drug was hard to be dissolved (solubility: about 4 µg/ml), it was eluted more rapidly than granules of Comparative Example 1 and mixed powder of Comparative Example 2. On the other hand, it was not observed a big difference in elution rate between granules of Comparative Example 1 and mixed powder of Comparative Example 2 wherein the citric acid was simply added to this granule.

**(0090)**

#### **Test Example 2**

Adsorption powder obtained in Example 1 and 2, granules obtained in Comparative Example 1 and kneaded powder obtained in Comparative Example 3 and 4 in an amount of 500 mg each were tabletted under the condition of tablet diameter 9.5 mm diam., compression pressure 1000 kg/cm<sup>2</sup> using auto graph (AG-5000B made by Shimazu Corporation) and tablet was obtained. Moreover, as control, porous cellulose used in Example 1, the crystalline cellulose used in Comparative Example 3 and citric acid used in Example 1, 2, Comparative Example 3 and 4 were tabletted with itself in the same way as described above. The degree of squeaking was evaluated by a withdrawing pressure withdraw tablet during the tableting from mortar, using the characteristic wherein the harder the squeaking phenomenon, the larger the withdrawing pressure and it is possible to evaluate squeaking by withdrawing pressure. The results are shown in Table 2.

**(0091)**

**Table 2**

	Withdrawing pressure (Kg)	Presence or absence of squeaking
Example 1	15	absent
Example 2	21	absent
Comparative Ex. 1	113	present
Comparative Ex. 3	158	present
Comparative Ex. 4	310	present

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porous cellulose	6	absent
Crystalline cellulose	7	absent
Citric acid	492	present

As it is clear from Table 2, granulation powder and kneaded powder of Comparative Examples were tabletted with some squeaking during the tableting, on the other hand, adsorption powder obtained in Example 1 and 2 had no problem such as squeaking for tableting, and tableting properties were extremely improved compared with granulation and kneaded powder of Comparative Example. Moreover, capping occurred when citric acid itself was tabletted.

(0092)

#### Example 5

Spherical porous cellulose (hole of structure B type, bulk specific gravity 0.1 g/ml, a diameter of 0.3 mm diam.) 120 g was introduced into a stainless steel ball and thereto was added dispersions dispersed vinpocetine 7.5 g to the solution of methacrylic acid-methyl methacrylate copolymer (Trade name Eudragit L100-55 made by Rohm Pharma, Germany) 22.5 g and ethanol 120 g, and it was admixed. The admixture was dried under vacuum at 40 degrees for 20 hours, thereafter, dried material was classified with a circle sieve of 32 mesh, and adsorption powder of 150 g was obtained.

(0093)

Adsorption powder 100 g was introduced into a flow type coating granulator (FD-3S made by Powrex Co.) and ethanol solution (concentration 10 wt.%) including ethyl cellulose of 8 pts.wt. (viscosity type 10 cp) and polyethyleneglycol 600 of 2 pts.wt. was sprayed with bottom spray system while controlling air-blow temperature of 60 degrees and product temperatures of about 35 degrees, and coating pharmaceutical preparation coated by 30 wt.% with respect to adsorption powder was obtained.

(0094)

#### Test Example 3

Elution properties of drug were examined in the same way as in Test Example 1, except using adsorption powder 150 mg and coated pharmaceutical preparation 195 mg obtained in

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Example 5 and the first liquid and the second liquid as test liquid. The results of adsorption powder are shown in Table 3 and the results of pharmaceutical preparation coating are shown in Table 4.

(0095)

**Table 3** (adsorption powder)

Elution time (mins)	Elution rate (%)				
	1	2	5	10	30
The first liquid	12	25	48	65	85
The second liquid	15	29	53	69	89

(0096)

**Table 4** (coated pharmaceutical preparation)

Elution time (mins)	Elution rate (%)				
	10	20	30	60	90
The first liquid	2	10	20	35	40
The second liquid	1	15	20	36	40

As it is clear from Table 3 and 4, adsorption powder and coated pharmaceutical preparation obtained in Example 5, in spite of vinpocetine being easily soluble with respect to the first liquid (solubility: at least 100 mg/ml) and barely soluble with respect to the second liquid (solubility: about 4 µg/ml), the same elution properties were shown in each case and elution properties of drug could be controlled by addition of acid (intestine soluble polymer).